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**(54) Medicinal aerosol formulation**

(57) The invention pertains to a medicinal drug preparation in the form of a suspension aerosol that contains a spray-dried product that [comprises] a medicinal substance and a surface active physiologically tolerated substance, which is insoluble in the liquefied propellant, and optionally a taste correcting agent and/or a conventional excipient in a liquefiable hydrogenated or partially hydrogenated fluorocarbon as the propellant. In addition, the invention pertains to a process for the [manufacture] of a medicinal drug preparation that contains medicinal substances that are locally active on the lungs and that are suitable for inhalation in order to treat diseases of the respiratory tract or asthma.

Modern aerosol technology, which is based predominantly on the use of safe propellants that are capable of being liquefied under moderate pressure, has resulted in a series of important advantages and it has also opened up numerous new possibilities in regard to applications. The following advantages are to be emphasized in detail in the following section.

Every pack that contains a compressed gas is an automatic dispensing device that permits the product to be removed or, as the case may be, to be applied in a form that is suitable for optimum action by means of finger pressure on an applicator. The quantity of product that is to be used can easily be adjusted - and can thus be rationally adjusted as well - via this type of control. A dispensing valve automatically takes over this quantity limitation function when removal in a constantly equal and small dose is appropriate.

The convenience of handling such packs that contain a compressed gas is a decisive advantage of this form of medicinal drug. The single-hand devices are practical in use and simple to handle. As a result of the automatically closing valve, the contents cannot flow out or be spilled. Volatile substances cannot evaporate and the contents cannot dry out. The gas-tight sealing of the pack prevents the entrance of air and the sources of contamination that are thereby possible via dust, moisture or germs. Products that are sensitive to oxidation can be packed with the exclusion of atmospheric oxygen. A pack containing a compressed gas also provides superb protection from light for sensitive active substances.

The product that is introduced into packs that contain a compressed gas frequently comprises a powdery substance (e.g. a medicinal substance) that is present in suspended form in the liquefied propellant along with a surface active substance that serves for the stabilization of the suspension, e.g. sorbitan trioleate, oleic acid or lecithin. So far, use has been made almost exclusively of fluorochlorohydrocarbons, e.g. trichlorofluoromethane (Frigen® 11), dichlorodifluoromethane (Frigen® 12), 1,2-dichlorotetrafluoroethane (Frigen® 114) and their mixtures, as the propellant for medicinal aerosols. The powder, which has to have a particle size that is as small as possible in order to prevent sedimentation, is dispersed in a significantly larger quantity of propellant. The proportion [that is represented by] the quantity of propellant must also amount to at least 85% by weight in order to reduce the risk of valve disorders and it will be

considerably above this value in many cases. We frequently find such aerosols in the form of aerosols for inhalation purposes.

Inhalation aerosols are suitable for administering medicinal substances for the therapy of diseases of the respiratory tract, e.g. for administering beta-sympathomimetic drugs, steroids, anticholinergic drugs, antihistamines, mast cell stabilizers such as cromoglycic acid or nedocromil, PAF antagonists, leukotriene antagonists, bradykinin antagonists or potassium channel activators for the local therapy of asthma. Inhalation aerosols are also suitable for the systemic therapy of diseases because the pulmonary epithelium possesses adequate permeability to low molecular medicinal substances. Pulmonary application by means of an inhalation aerosol is especially suitable for highly effective medicinal substances, e.g. peptides and proteins such as insulin, LHRH analogs, oxytocin, vasopressin analogs, calcitonin analogs or interferon (see e.g. Banga and Chien, Int. J. Pharm. 48, 15-50 (1988)). Suspension aerosol formulations of LHRH analogs with a fluorochlorohydrocarbon as the propellant are described in e.g. EP-A-0 510 731.

Discussions regarding the cause of the damage to the ozone layer by fluorochlorohydrocarbons (FCHC) have led to the situation in which the use of these substances has been restricted, or even partially banned, in many countries. It is known from research studies that one of the causes, which lead to damage to the ozone layer, is the reaction of ozone with radicals that are produced from the chlorine atoms of FCHC [fluorochlorohydrocarbons]. Thus propellants that are not ozone-damaging, e.g. carbon dioxide, dinitrogen oxide, dimethyl ether, short chain hydrocarbons (propane or butane) or hydrogenated fluorocarbons (HFC), have been used recently for aerosols.

Propellant gases, which can be liquefied under pressure at room temperature and which are safe, toxicologically innocuous and free from side effects in the case of inhalation or topical use, are especially suitable as propellants for pharmaceutical aerosols. These properties apply, in particular, to hydrogenated fluorocarbons (HFC) such as e.g. tetrafluoroethane (R134a) and heptafluoropropane (R227), whereby heptafluoropropane is more suitable as a result of its lower vapor pressure, namely approximately 4 bar, at room temperature because a pressure-reducing addition can be dispensed with. Because of its higher vapor pressure, namely 6 bar, at room

temperature, tetrafluoroethane cannot be used as the sole propellant because, at 50°C, it exceeds the highest permissible pressure of 12 bar for aluminum cans in accordance with TRG300 (the Technical Guidelines for Gases) with its pressure of approximately 13 bar.

The previously used technology for the preparation of medicinal suspension aerosols is based on the solubility of the surface active substances in the liquefied propellant (the medicinal substance is suspended in the propellant). Because of their higher polarity, this property is no longer available when using the new alternative propellants such as tetrafluoroethane or heptafluoropropane. This means that formulations with fluorochlorohydrocarbons cannot be switched with ease merely by exchanging the propellant for hydrogenated fluorocarbons as is described in EP-A-0 513 099, EP-A-0 518 600, EP-A-0 518 601 and EP-A-0 550 031. Stable suspensions cannot be prepared in this way with the surface active substances that have been used so far in inhalation aerosols.

According to EP-B-0 372 777 and EP-A-0 499 344, use is therefore made of co-solvents with a higher polarity, such as e.g. ethanol, in order to achieve adequate solubility of the surface active substance in the liquefied propellant (HFC) [hydrofluorocarbon]. The use of other surface active substances, which are soluble in the liquefied propellant (HFC) [hydrofluorocarbon] but which have not been used so far in medicinal aerosols, is described in EP-A-0 504 112 (monoacetylated or diacetylated monoglycerides), and in EP-A-0 536 204, EP-A-0 513 127 and EP-A-526 481 (fluorinated surfactants), and in EP-A-0 536 235 (block copolymers assembled from ethylene oxide and propylene oxide, and also polysorbates), and in EP-A-0 534 731 (polyvinylpyrrolidone and poly(vinyl alcohol)). However, the designated substances have the decisive disadvantage that they have not been tested toxicologically for inhalation-based use or that they have even proven unsuitable because of tissue damage.

In addition, a process is described in the patent applications WO 92/08446 and WO 92/08447 in the case of which active substances are coated with the surface active substance. The starting point in this connection is a pre-micronized active substance that is suspended in a solution of the surface active substance in an organic solvent, such as e.g. isopentane, in which the active substance is practically insoluble. The solvent is removed after a certain time. The

active substances that have been modified in this way can be suspended in hydrogenated fluorocarbons (HFC) with the addition of a co-solvent, if required. A disadvantage of this process is that the pre-micronized active substance has to be suspended and re-dried. Agglomeration of the particles can arise in this way. The process does not ensure a uniform distribution of the surface active substance. Moreover, the use of an additional organic solvent, such as isopentane, is to be assessed negatively.

The objective that now forms the basis of the invention is to formulate a stable suspension dispensing-type aerosol for medicinal use that contains a pharmaceutically active substance, a physiologically tolerated surface active substance, e.g. sorbitan trioleate, oleic acid and lecithin, that is insoluble in the liquefied propellant, and optionally a taste correcting agent, e.g. a sweetener, such as saccharin, acesulfam K or aspartam, or an etherial oil, a generally conventional excipient from the group of sugars or sugar alcohols, such as lactose, glucose or mannitol, if required as well as a hydrogenated fluorocarbon, preferably heptafluoropropane (R227), as the propellant.

This objective is accomplished, in accordance with the invention, by using spray drying to transform the active substance and the surface active substance, optionally together with the designated additional excipients, into a form in which they are mutually present in a matrix in a finely distributed form. Surprisingly, it has been found that this spray dried product then forms a fine stable homogeneous suspension in the liquefied propellant without further additions.

The invention thus pertains to a medicinal drug preparation in the form of a suspension aerosol, characterized by the feature that it contains

- a) a spray-dried product that comprises a medicinal substance and a physiologically tolerated surface active substance, which is insoluble in the liquid propellant, and optionally a taste correcting agent and optionally a generally conventional physiologically tolerated excipient, and
- b) a liquefiable hydrogenated or partially hydrogenated fluorocarbon as the propellant.

The active substances and the excipients (including the surface active substances) are present in the spray dried product in a finely divided form in a matrix. A fine stable homogeneous suspension is formed after adding the propellant. The particles of the product have a particle size that is conventional for aerosols.

In addition, the invention pertains to a process for the manufacture of a medicinal drug preparation in the form of a suspension aerosol, characterized by the feature that the medicinal substance, the physiologically tolerated surface active substance and, optionally, a taste correcting agent and, optionally, further generally conventional physiologically tolerated excipients are dissolved in a suitable solvent, and the solution that is obtained is subjected to spray drying, and the spray dried product is packaged in a pack containing a compressed gas, and this [pack] is sealed off with a dispensing valve, and a quantity of the liquefiable hydrogenated or partially hydrogenated fluorocarbon, which is required for the formation of the suspension aerosol, is fed in.

As far as the medicinal substances are concerned, consideration can be given to those that are locally active on the lungs and that are suitable for inhalation, i.e., for example, medicinal substances for the treatment of diseases of the respiratory tract or asthma, such as beta-sympathomimetic drugs, steroids, anticholinergic drugs, antihistamines, anti-allergic preparations, mast cell stabilizers such as cromoglycic acid or nedocromil, PAF antagonists, leukotriene antagonists, bradykinin antagonists or potassium channel activators.

Spray drying is also suitable for pharmaceutical active substances that cannot be micronized by conventional methods, such as grinding, and thus cannot be transformed into the particle size that is necessary for inhalation. This applies especially to peptides and proteins that are obtained by freeze drying and that are present in amorphous form.

Thus as far as the active substances are concerned, consideration can also be given to peptides and proteins of natural or synthetic origin and their physiologically tolerated salts. Mention may be made of the following as examples: insulin, LHRH analogs, oxytocin, vasopressin analogs, calcitonin analogs and interferon and their physiologically tolerated salts.

As far as the medicinal substance is concerned, the suspension aerosols in accordance with the invention preferably contain an insulin, a bradykinin antagonist, an LHRH analog such as buserelin, or their physiologically tolerated salts.

The suspension aerosols in accordance with the invention are suitable, in particular, for the treatment of asthma and contain e.g. the bradykinin antagonist icatibant (= H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH (HOE 140)) or an icatibant salt or the potassium channel activator rilmakalim ((+)-(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-phenylsulfonylchroman hemihydrate).

Sorbitan trioleate, oleic acid or lecithin are especially preferred as the surface active substances. All natural lecithins, such as egg lecithin or soy lecithin, partially hydrogenated and hydrogenated lecithins and also highly purified phosphatidylcholine, are suitable as the lecithin.

Suitable taste correcting agents are e.g. sweeteners, such as saccharin, aspartam and acesulfam K, or etherial oils.

As is also the case with the active substances and the surface active substances and the taste correcting agents, the generally conventional physiologically tolerated excipients must be soluble in the communal solvent. The nature of these excipients is therefore governed by the solvent that is used. Excipients from the group comprising the sugars and the sugar alcohols, such as lactose, glucose or mannitol, are especially suitable.

The spray dried product contains one or more active substances, one or more surface active substances and, optionally, one or more additional excipients and taste correcting agents.

Heptafluoropropane (R227), for example, and tetrafluoroethane (R134a), preferably in admixture with R227, are suitable as propellants.

Mixtures comprising the lower alcohols (with up to 6 C atoms) or ketones and water are, for example, suitable as the communal solvent for the components of the spray dried product.

The proportion of the active substance in the spray dried product is governed, in particular, by the amount of the desired addition.

The proportion of surface active substance that is distributed in the active substance matrix is relatively low and amounts to e.g. 0.01 to 1.0% by weight or, preferably, 0.05 to 0.5% by weight, based on the proportion of the active substance.

Spray drying is carried out in accordance with the usual methods as described in the literature (see, for example, J. Broadhead et al., Drug Development and Industrial Pharmacy, 18, 1169-1206 (1992)). It is preferably carried out at an elevated temperature, whereby the [temperature] level is dependent, *inter alia*, on the active substance that is used, and the solvent.

The particles of the active substance acquire a spherical aerodynamic shape as a result of the process of spray drying; as a result of this, their movement in the stream of air while breathing is affected favorably, and the proportion of particles that have access to the lungs is thereby increased. In addition, the forces of adhesion and agglomeration are reduced both in the suspension and also during the spraying process. The process of spray drying in order to prepare powders for use via inhalation is already known from the patent specifications GB 1 520 248 and GB 1 569 612. Here, however, only the pure active substances were spray dried without adding surface active substances, taste correcting agents or additional excipients, and formulation then took place in the form of a powder for inhalation purposes but not in the form of a suspension aerosol.

The invention will be elucidated by means of the following examples.

#### Example 1

1968 mg of icatibant acetate, 2.0 mg of S100 soy lecithin (Lipoid K.G.) and 30 mg of saccharin are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 110°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an

Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 100 µg of the medicinal substance, per application.

### Example 2

430 mg of icatibant acetate, 3566 mg of lactose and 4 mg of hydrogenated egg lecithin (EPC-3, Lipoid K.G.) are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 90°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 10 µg of the medicinal substance, per application.

### Example 3

1968 mg of icatibant acetate, 2 mg of sorbitan trioleate and 30 mg of aspartam are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 110°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the

suspension, which contains 100 µg of the medicinal substance, per application.

Example 4

1000 mg of human insulin, 2 mg of S100 soy lecithin and 1000 mg of lactose are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 90°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 50 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which corresponds to 31.U. [translator: 3 I.U.?] of insulin, per application.

Example 5

1998 mg of buserelin acetate and 2 mg of S100 soy lecithin are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 90°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 100 µg of the medicinal substance, per application.

Example 6

1998 mg of rilmakalim hemihydrate and 2.0 mg of S100 soy lecithin are dissolved to give a clear solution in an ethanol/water mixture (50% W/W) and then spray dried at 100°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 100 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 1000 µg of the medicinal substance, per application.

Example 7

1998 mg of icatibant acetate and 2.0 mg of sorbitan trioleate (Span<sup>®</sup>85) are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 100°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 100 µg of the medicinal substance, per application.

Example 8

1998 mg of icatibant acetate and 2.0 mg of oleic acid are dissolved to give a clear solution in an acetone/water mixture (25% W/W) and then spray dried at 80°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a

fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100  $\mu$ l of the suspension, which contains 100  $\mu$ g of the medicinal substance, per application.

#### Example 9

200 mg of salbutamol, 2.0 mg of S100 soy lecithin and 1798 mg of lactose are dissolved to give a clear solution in an ethanol/water mixture (25% W/W) and then spray dried at 80°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 50 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which had been prepared in accordance with the process, contains 100  $\mu$ l of the suspension, which contains 50  $\mu$ g of the medicinal substance, per application.

#### Example 10

1998 mg of prednisolone and 2.0 mg of S100 soy lecithin are dissolved to give a clear solution in an ethanol/water mixture (50% W/W) and then spray dried at 80°C under inert conditions (N<sub>2</sub>) in a spray drying apparatus. The product is thereby generated in the form of a fine white powder. The powder is introduced into an Alumonobloc can, which is intended for aerosols that are to be dispensed, at the rate of 10 mg per can; the can is sealed with a dispensing valve and then filled with 10 g of R 227 via the dispensing valve. A fine homogenous suspension of primary particles of the medicinal substance in R 227 is produced immediately after the filling operation. A sprayed burst of the inhalation aerosol (suspension aerosol), which

had been prepared in accordance with the process, contains 100 µl of the suspension, which contains 100 µg of the medicinal substance, per application.

### Patent claims

1. A medicinal drug preparation in the form of a suspension aerosol, characterized by the feature that it contains
  - a) a spray-dried product that comprises a medicinal substance and a physiologically tolerated surface active substance, which is insoluble in the liquefied propellant, and optionally a taste correcting agent, and optionally a generally conventional physiologically tolerated excipient, and
  - b) a liquefiable hydrogenated or partially hydrogenated fluorocarbon as the propellant.
2. Process for the manufacture of a medicinal drug preparation in the form of a suspension aerosol in accordance with Claim 1, characterized by the feature that the medicinal substance, the physiologically tolerated surface active substance, and optionally a taste correcting agent, and optionally further generally conventional physiologically tolerated excipients are dissolved in a suitable solvent, and the solution that is obtained is subjected to spray drying, and the spray dried product is packaged in a pack containing a compressed gas, and this [pack] is sealed off with a dispensing valve, and a quantity of the liquefiable partially hydrogenated or hydrogenated fluorocarbon, which is required for the formation of the suspension aerosol, is fed in.
3. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that it contains medicinal substances that are locally active on the lungs, and that are suitable for inhalation in order to treat diseases of the respiratory tract or asthma.

4. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that it contains a peptide or a protein or their physiologically tolerated salts as the medicinal substance.
5. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that it contains icatibant or its physiologically tolerated salt.
6. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that the surface active substance is sorbitan trioleate, oleic acid or lecithin.
7. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that the propellant is heptafluoropropane.
8. A medicinal drug preparation in accordance with Claim 1, characterized by the feature that the taste correcting agent is a sweetener and/or an etherial oil, and the additional excipients are selected from the group comprising the sugars and sugar alcohols.

European Patent  
Office

Application number  
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## EUROPEAN SEARCH REPORT

## DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. <sup>6</sup> )
A	WO-A-91 16882 (LIPOSOME TECHNOLOGY, INC.) * Page 4, Line 28 - Page 5, Line 39* *Page 15, Line 6 – Line 24*	1-4, 6	A61K9/00
A	DE-A-41 23 663 (DR. WILLMAR SCHWABE GMBH & CO.) * the entire document*	1-4, 6, 7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. <sup>6</sup> ) A61K

The present search report has been drawn up for all claims.

Place of search	Date of completion of the search	Examiner
THE HAGUE	February 21, 1995	Ventura Amat, A

## CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone  
 Y: Particularly relevant if combined with another document of the same category  
 A: Technological background  
 O: Non-written disclosure  
 P: Intermediate document  
 T: Theory or principle underlying the invention  
 E: Earlier patent document but published on, or after, the filing date  
 D: Document cited in the application  
 L: Document cited for other reasons  
 &: Member of the same patent family, corresponding document